Evaluation of Anticonvulsants for Possible Use in Neuropathic Pain

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Abstract: Neuropathic pain is a kind of pain related with functional abnormality of neurons. Despite large progress in pharmacotherapy, neuropathic pain is still considered an unmet need. Nowadays, there are few drugs registered for this condition, such as pregabalin, gabapentin, duloxetine, carbamazepine, and lidocaine. Among them, pregabalin, gabapentin and carbamazepine are well known antiepileptic drugs.

Among the group of new antiepileptic drugs, which are addressed to 1% of human world population suffering from seizures, it turned out that 30% of the seizures resistant to pharmacotherapy has not enough market to justify the costs of drug development. Therefore, it is already a phenomenon that researchers turn their projects toward a larger market, related with possible similar mechanism.

Anticonvulsant mechanism of action is in the first place among primary indications for drugs revealing potential analgesic activity. Therefore, many drug candidates for epilepsy, still in preclinical stage, are being evaluated for activity in neuropathic pain.

This review is focusing on antiepileptic drugs, which are evaluated for their analgesic activity in major tests related with neuropathic pain. Relation between structure, mechanism of action and result in tests such as the Chung model (spinal nerve ligation SNL), the Bennett model (chronic constriction injury of sciatic nerve CCI) and other tests are considered. The first examples are carbamazepine, gabapentin, and lacosamide as drugs well established in epilepsy market as well as drug candidates such as valnoctamide, and other valproic acid derivatives, novel biphenyl pyrazole derivatives, etc. Moreover, clinical efficacy related with listed animal models has been discussed.

Keywords: Allodynia, analgesic, anticonvulsant, CCI, epilepsy, hyperalgesia, neuropathic pain, preclinical, seizures, SNL.

I. INTRODUCTION

Neuropathic pain is a kind of pain caused by functional abnormality of neurons, related with their damage. Despite large progress in pharmacotherapy, neuropathic pain as an indication is still considered an unmet need, since 50% of patients suffer from the pain despite treatment [1]. Nowadays, there are few drugs registered for this condition, such as amitriptyline [2], pregabalin [3], gabapentin [4], duloxetine [5], carbamazepine [6], lidocaine [7], lamotrigine [8], and opioids [9]. Among them, pregabalin, gabapentin, carbamazepine, and lamotrigine are well known and well established antiepileptic drugs (AEDs). Furthermore, gabapentin is considered the leading drug in neuropathic pain treatment.

Among the group of new AEDs, which are addressed to 1% of human world population suffering from seizures, it turned out that 30% of the seizures resistant to pharmacotherapy has not enough market to justify the costs of drug development. Even though the number of epileptic conditions is still rising, as epileptogenesis becomes better understood, the new conditions such as myoclonic astatic seizures, Lennox-Gastaut syndrome, or severe myoclonic epilepsy in infancy, or even epilepsy in pregnancy or childhood are a difficult market to develop new drugs. Most recent AEDs have been developed through the Antiepileptic Drug Development Program (ADD) at National Institutes of Neurological Disorders and Stroke, (NINDS), National Institutes of Health (NIH), Rockville, MD, USA under supervision of prof. James P. Stables or with some support from the Institute [10].

Well known AEDs revealing certain mechanisms involved in the genesis and maintenance of hyperexcitability, are an important area of progress in the research and therapy of neuropathic pain. Currently, among primary indications for drugs revealing potential analgesic activity in neuropathic pain in the first place most often there is anticonvulsant mechanism of action. Therefore, many drug candidates for epilepsy, still in preclinical stage, are being evaluated for activity in neuropathic pain. Mechanisms of action represented by analgesic drugs effective in neuropathic pain are also typical in most cases of antiepileptic drugs:

- ion channel modulators (sodium, potassium, and calcium),
- GABA (γ-aminobutyric acid) modulators,
- glutamate receptor modulators,
- monoamine modulators,
- cannabinoid receptor modulators,
- opioids, and
- topical capsaicin treatments.

Among the above mechanisms, the major ion channel modulators and GABA modulators are typical mechanisms of action of AEDs.

Neuropathic pain has been considered as a progressive nervous system disease in which spread of pain generating mechanisms is due to the biochemical reactions in the nervous system [11]. Some systemic reviews have drawn attention to new information of molecular, biochemical and neuroanatomical mechanisms of neuropathic pain which have identified a potential therapeutic target for the treatment of persistent pain.

Peripheral neuropathic pain may be caused by mechanical nerve injury, metabolic disease, neurotropic viral disease, neurotoxicity or tumor. Those factors may result in pathophysiological changes in peripheral as well as in central nervous system. Spinal cord injury, stroke or multiple sclerosis remain most common reasons of central neuropathic pain. Differentiation of the peripheral and central sites of the pain is possible considering only the etiology because those mechanisms are initiators of the cascade of changes in all parts of nervous system. Another possible etiology of persistent pain is related with inflammatory mechanisms but undoubtedly there is a fundamental difference in the neuronal pathways responsible for neuropathic and inflammatory pain so they remain distinct in terms of their eiology and clinical features [12]. Inflammation involves accumulation of endogenous factors (such as mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts) which can infiltrate the changed nerves. Additionally, nociceptors express one or more cell-surface receptors capable of responding to these agents, which together lead to enhancing excitability of the nerve fiber. Reducing inflammatory pain is

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commonly reached by inhibition of synthesis or accumulation of those pro-inflammatory factors. Another approach is to block the action at the nociceptor. The progress has been made in identifying new target molecules in possible therapeutic strategies of treating inflammatory pain. There are nerve growth factor (NGF), interleukin-1β (IL-1β), IL-6, tumor necrosis factor α (TNF-α) and transient receptor potential (TRP) cation channels among them are nociceptor channels responsible for sensitivity to heat – TRPV1 (also known as vanilloid receptor or capsaicin receptor) or chemical stimuli – TRPA1 [13].

Great progress has been also made in understanding mechanisms implicated in central site of neuropathic pain. Among others, alteration in glutamatergic neurotransmission/NMDA receptor-mediated sensitization, loss of GABAergic and glycinergic controls (disinhibition) and glial-neuronal interactions have been described [13]. Undoubtedly voltage-gated sodium channels (Na_V), especially their specific isoforms ($Na_V1.1$-$Na_V1.9$), constitute an attractive target in pharmacotherapy of neuropathic pain. It has been shown in both animal studies and human tissues that nerve injury induces dynamic regulation of sodium channel expression in dorsal root ganglion [14]. But still it is not clearly stated which sodium channel isoforms are responsible for human neuropathic pain syndromes. However, $Na_V1.8$ and $Na_V1.3$ are promising molecules [15]. Recent studies showed that T-type (Ca_V3) channels are also in interest as target molecules in neuropathic pain [16].

Neuropathic pain can be divided into three major disorders: diabetic neuropathic pain (DNP), post-herpetic neuralgia (PHN), and Human Immunodeficiency Virus-associated neuropathic pain (HIVNP). Approximately 20-24% of diabetes patients suffer from DNP [17]. Other neuropathies to be mentioned are trigeminal neuralgia, thalamic syndrome, phantom limb pain, tabetic pain, *etc*. The prevalence in the USA is 0.054% for DNP, and 0.185% for PHN [18].

Preclinical evaluating tests for neuropathic pain are based on mice or rats and involve surgery or chemical stimuli. Animal models of pain have been designed for proper evaluation of drug candidates for potential use in various pain types. The following list is limited to the kinds of assays which have been used for evaluation of antiepileptic drugs.

- Tight Ligation of Spinal Nerves (SNL-Spinal Nerve Ligation), *i.e.* the Kim and Chung model, Chung model – the procedure involves spinal L5 or L5-L6 nerves ligation in rats; the test allows assessment of activity in alleviating mechanic allodynia and mechanic hyperalgesia, as well as thermal hyperalgesia. The pain is developed in the hind limb at the side of the ligation. The symptoms remain for 49 days and the test is concerned as a model for acute pain [19].

- Loose Ligation of the Sciatic Nerve (CCI-chronic constriction injury), *i.e.* the Bennett and Xie model, Bennett model – the procedure is performed in rats and causes development of inflammation as a response to presence of the thread, which in turn leads to damage of the neuron and development of neuropathic pain. The phenomena related with the model are mechanic allodynia, mechanic hyperalgesia, and thermal hyperalgesia. The neuropathic pain is developed up till 2 weeks after the procedure. The CCI model is concerned as a test for chronic pain [19].

- Streptozocin test – the test for diabetic neuropathy in mice or rats; the animals that have developed diabetes post streptozocin *i.p.*(intraperitoneal) administration, are administered a tested substance and response to nociceptive stimuli is observed [20].

Additionally, the formalin test is usually performed to study whether the compound possesses any analgesic activity. The test involves injection of formalin to a mouse or a rat paw which results in neuronal damage, exhibited by two phases of pain response: acute phase and inflammatory phase [21, 22].

As the tests used for verification of analgesic activity must induce pain in animals, in order to spare the animals, the negative controls are often represented by:

- a group of animals which have received injection with placebo,

- sham-operated rats (in the CCI and SNL models) – the animals have the nerve isolated but not ligated, or

- the sensitivity is tested at the opposite side of the ligation.

Nociception is related with the following phenomena:

- allodynia – pain caused by non-nociceptive stimulus, *e.g.* due to lowering sensitivity threshold of a receptor. Tactile allodynia occurs probably due to central changes triggered by increased activity of nociceptors but in contrast, more recent findings suggest that nociceptors are not required for the induction of mechanical hypersensitivity[23].

- analgesia – lack of feeling pain in place of nociceptive stimulus;

- anesthesia – lack of all perception types;

- hyperalgesia – increased sensitivity to pain; the mechanism of hyperalgesia is probably connected with functions of thalamus, anterior cingulate cortex and central nucleus of the amygdala [23].

- neuralgia – attacks of short time pain not related with any cause, without damage of the nervous system;

- paresthesia – wrong perception of a pain stimulus.

The observed allodynia types in the models involve:

- cold allodynia – response to ethyl chloride spray stimulation – the total time of licking the limb is added; or placing a drop of acetone on the foot and observing its withdrawal; acetone is placed 5 times, each time after a 5 min. break; the endpoint is the amount of acetone followed by withdrawal of the limb * 100,

- tactile allodynia – response to touch by von Frey filaments respective to various strengths and masses; the endpoint is number of touches followed by withdrawal of the limb * 100.

The aim of this review is to show antiepileptic drugs which are evaluated for their analgesic activity in major tests related with neuropathic pain. Relation between structure, mechanism of action and result in tests such as the Chung model – the most popular test, the Bennett model and other tests are considered.

Moreover, some authors have approached similar reviews in the past [12, 13, 23, 24], however, large progress has been made in terms of knowledge underlying molecular and cellular mechanisms of disease development as well as possible mechanisms of action of potential drugs, and clinical efficacy of drugs.

II. ANTIEPILEPTIC DRUGS AND THEIR EVALUATION FOR PAIN TREATMENT

The currently used antiepileptic drugs have been secondarily evaluated in neuropathic pain models, which means that neuropathic pain is their second indication. This could be the reason why such compounds show modest efficacy in neuropathic pain. However, new drugs have some advantages, such as improved profile and pharmacokinetics and more favorable tolerability [25]. This is why this review is focused on comparison of the activity in epilepsy with activity in neuropathic pain in the same species and routes of administration. The drugs have been grouped with mechanisms of

action and secondarily by structure similarities. The results presented in the text are summarized in Table **1**.

1. Ion Channel Modulators

Ion channel modulators exhibit great potential in neuropathic pain. Lacosamide, which represents sodium channel blockers, has become very popular AED in the pain treatment [15]. However, retigabine – a potassium channel opener, also turned out to be active in pain models, as shown below. Other channels related with analgesic and anticonvulsant activity are calcium channels.

Voltage-gated sodium channels have been shown to play a critical role in neuropathic pain. Still, their non-specific inhibition is also a mechanism of action for the oldest antiepileptic drugs. Within the process of neuropathic pain formation, due to GDNF (glial cell derived neurotrophic factor) enhanced activity, voltage-gated sodium channel (Na_V) subtype 1.3 is induced, causing susceptibility to stimuli. Moreover, in the non-destructed part of the neuron – $Na_V1.7$ and 1.8 channels are overexpressed [18]. This is why sodium channels are a promising target for drug candidates, however, for the ones that are selective enough. Recent studies have shown that by targeting specifically subtypes $Na_V1.1$ and 1.2 a molecule can reduce seizures [26] and not neuropathic pain. Therefore, specificity towards $Na_V1.3$, 1.7, and 1.8 versus $Na_V1.1$ and 1.2 could differentiate between analgesics and antiepileptic drugs, respectively.

Inhibition of sodium channels is the mechanism seen for the very first antiepileptic drugs and for some novel drug candidates: carbamazepine, oxcarbazepine, lamotrigine, lacosamide, zonisamide, topiramate, and biaryl pyrazoles. Opening potassium channels is a main mechanism for retigabine, but the biaryl pyrazole derivative by Merck also exhibits some affinity. Calcium channels are influenced by zonisamide, topiramate, and the mentioned biaryl pyrazole derivative, and the $\alpha 2\delta$ subunits of channels are inhibited by pregabalin and gabapentin.

Carbamazepine and Oxcarbazepine

Carbamazepine (5*H*-dibenzo[b,f]azepine)-5-carboxamide) (Fig. **1**) exhibits ED_{50}s (effective dose in 50% animals) in MES (maximum electroshock seizures) 7.81 mg/kg b.w. (body weight) mice, *i.p.* and 17 mg/kg b.w. mice, *p.o.*(*per os*) [10, 27] (Table **1**). In humans, this iminostilbene derivative is active in simple partial, complex partial, and generalized tonic-clonic seizures, while inactive or deleterious in absence or myoclonic seizures [28]. It is a drug of first choice in the treatment of epilepsy, also during pregnancy. Its monotherapy in mothers during conception causes malformations only in 1.3%-8.7% newborn children up to 1 year of age, if mothers had been taking doses ranging from <400 mg/day-1000 mg/day [29].

This AED administered *s.c.* (subcutaneously) to rats, significantly reduces spontaneous neuronal activity in the Chung model (SNL) at doses 0.5-22.5 mg/kg b.w. [30]. It is also active in reduction of inflammatory exudate caused by implantation of carrageenan soaked sponges in rats with ED_{50} of 27.5 mg/kg b.w. (rats, *p.o.*) [31], while the anti-inflammatory activity is not necessarily related with the anticonvulsant mechanism of action. The analgesic activity in humans has been widely discussed, since the first report on activity of carbamazepine in trigeminal neuralgia was reported in 1962 by Blom and carbamazepine is now considered a drug of choice for this condition [32, 33].

Oxcarbazepine (10,11-dihydro-10-oxo-5*H*-dibenz[b,f]azepine-5-carboxamide) (Fig. **1**), a well known 10-oxoderivative of carbamazepine, inhibits voltage-gated sodium channels, which is the main mechanism of action in seizures management. Its additional mechanisms of action, apart from blocking voltage-gated sodium channels, are increase of potassium conductance and modulation of calcium channels. Preclinical evaluation in epilepsy reveals ED_{50}

6.1 mg/kg b.w. in rats, *i.p.* with TD_{50} (toxic dose in 50% animals, measured by rotarod) 40.1mg/kg b.w. (rats, *i.p.*) [34]. More data are presented in Table **1**. Oxcarbazepine is a second generation antiepileptic drug with proved efficacy in monotherapy and combination therapy in managing partial epileptic seizures. It is relatively better tolerated than carbamazepine [35].
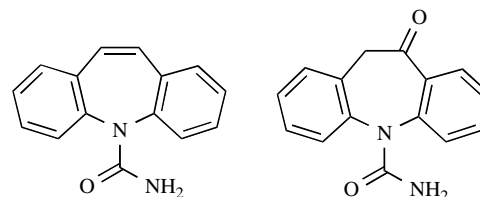

Fig. (1). Chemical structures of carbamazepine and oxcarbazepine.

Oxcarbazepine was proved to be active in the Chung model in a dose-dependent manner, 15 min. after *i.p.* administration of 10-50 mg/kg b.w. (Table **1**) [35]. Therefore, it can be effective in various neuropathic pain conditions that are accompanied by allodynia or hyperalgesia. However, it was not proved whether the analgesic activity mechanism depends on Na_V channels. Other mechanisms related with pain models for carbamazepine and oxcarbazepine are associated with NMDA (*N*-methyl-*D*-aspartic acid) receptor [31], as well as A1 (adenine) receptor [36] which possibly revitalizes the opioid system [37]. The rationale for use of oxcarbazepine was also discussed in humans and its activity in pain related with trigeminal neuralgia has been proved, as well as in diabetic neuropathy [33, 38, 39]. However, this drug failed in another study for DNP [40].

Its efficacy at doses 900-2100 mg/day is comparable to carbamazepine taken 400-1200 mg/day in trigeminal neuralgia. Also in clinical trials – oxcarbazepine proved to be better tolerated than carbamazepine as fewer incidents of vertigo, ataxia, dizziness, and fatigue were reported [33].

Lamotrigine

Lamotrigine (6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, LTG) (Fig. **2**) is a well known anticonvulsant, whose mechanism of action is basically inhibition of voltage- and use-dependent sodium channels and calcium channels, supported by inhibition of release of excitatory aminoacids. In preclinical tests it proved efficacy in MES at ED_{50}=33.2 µM/kg b.w. (mice, *i.p.*), in 6Hz test ED_{50}=100.4 µM/kg b.w. (mice, *i.p.*, 32 mA), in corneal kindling ED_{50}=37.1 µM/kg b.w. (mice, *i.p.*) and in hippocampal kindling ED_{50}= 61.3 µM/kg b.w. (rats, *i.p.*). As hippocampal kindling is a model for epileptogenesis, the AED should slow down development of the disease in patients [41]. Lamotrigine is also active in sound induced seizures (AGS, audiogenic seizures) in Frings mice *i.p.* with ED_{50} of 2.39 mg/kg b.w. TD_{50} in rotarod test is 30 mg/kg b.w. (mice, *i.p.*) and 411 mg/kg b.w. (rats, *p.o.*) [42, 43]. Clinical trials in epilepsy show that lamotrigine is similarly effective to carbamazepine. However, it may have a more favorable long-term effect on cognitive function when compared to carbamazepine (in terms of phonemic verbal fluency and stroop color-word interference) [44]. Clinical safety of this AED when used in pregnancy is also comparable to carbamazepine – it causes malformations only in 1.7%-4.5% newborn children up to 1 year of age, if mothers had been taking doses ranging from <300 mg/day-≥300 mg/day [29]. Lamotrigine also can be used in absence seizures in children [45].
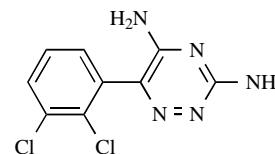

Fig. (2). Chemical structure of lamotrigine.

Lamotrigine was active in the Chung model with ED_{50} of 12 mg/kg b.w. (originally 47 μM/kg) rats, *p.o.* [46], compared to MES ED_{50} 1.26 mg/kg b.w. rats, *p.o.* and 7.47 mg/kg mice, *i.p.* (Table **1**).

It is more effective than carbamazepine in clinical trials for use in trigeminal neuralgia. The recommended doses are 25 mg/day, increased by 25 mg every seventh day until the effect or until maximum dose 400 mg/day is achieved [47]. Lamotrigine has been shown to relieve pain associated with DNP, central post-stroke pain and chemotherapy-induced neuropathic pain [48-50]. Additionally, the analgesic efficacy of lamotrigine in the treatment of painful HIV-associated distal sensory polyneuropathy (DSP) was stated [51]. The typical adverse event for this drug is skin rash, and the chance for it increases with the dose. Other side effects are headache and cough [45].

Lacosamide

Lacosamide (harkoseride, SPM927, ADD 234037, 2(*R*)-acetamido-*N*-benzyl-3-methoxypropionamide) (Fig. **3**) exerts activity by means of selective enhancement of slow inactivation of voltage-gated sodium channels [52]. The enantiomer *R* is active in MES at dose 4.5 mg/kg b.w. (mice, *i.p.*) and 3.9 mg/kg b.w. (rats, *i.p.*). Lacosamide is also active in audiogenic seizures (Frings mice) and kindling models as well (Table **1**) [53]. This AED was found active in cases of partial seizures and in simple motor status epilepticus (with levetiracetam) [54] as well as in refractory nonconvulsive status epilepticus [55].
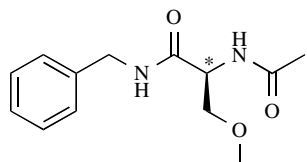
Fig. (3). Chemical structure of lacosamide.

The analgesic activity of lacosamide has been widely examined. Its only mechanism of action is block of sensory neuronal Na_V channels, since it does not bind significantly to any of over 50 other targets at 10 μM concentration [15, 56]. Lacosamide proved to be active in models for cancer-related pain [57], in the Chung model [58, 59] and the streptozocin model for diabetic neuropathy in the following tests: cold bath test (thermal allodynia), hot plate test (thermal allodynia and hyperalgesia), paw pressure withdrawal test (mechanical hyperalgesia), and brushing test (dynamic allodynia) [60]. The preclinical properties have been subject to other reviews as well [53]. Its activity in inflammatory pain also has been proved in the formalin test, at dose 32 mg/kg b.w. (mice, *i.p.*), in the carrageenan-induced thermal and mechanical hyperalgesia in rats (at 32 mg/kg b.w. and 8 mg/kg b.w., respectively, *i.p.*) and adjuvant-induced arthritis in rats (at 40 mg/kg b.w.) [61].

Consistently with activity in the streptozocin model, lacosamide is also active in DNP in humans with proved efficacy at doses 200-600 mg/day, while its most common adverse events are dizziness, headache, nausea, and – at 600 mg/day – tremor [62, 63]. Surprisingly, subsequent trials have failed to find an effect [64].

Zonisamide

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide, ZSM) (Fig. **4**) protects against seizures *via* inhibition of Na_V channels (produces use- and voltage dependent blockade and slows the rate of recovery) as well as T-type calcium channels. Other additional mechanisms have an influence on neurotransmitter systems, *i.e.* GABAergic (through binding to GABA receptors and influencing GABA transport), dopaminergic and serotoninergic (increasing extracellular levels of dopamine or serotonin), glutaminergic, and cholinergic. It also inhibits carbonic anhydrase,which is too weak to influence its anticonvulsant activity, but affects its pharmacokinetics [65-67].

Consistently with multiplicity of mechanisms of action, ZSM is also active in many animal models, exhibiting ED_{50}=19.6 mg/kg b.w. (mice, *p.o.*) and ED_{50}=7.9 mg/kg b.w. (rats, *p.o.*) in MES, activity in hippocampal seizures (rats) and amygdala kindled seizures in rats and in cats [68]. The molecule was developed primarily by Dainippon, recently by Elan and Eisai, and presents broad spectrum activity in clinical trials: adjunct therapy in partial and generalized (tonic-clonic) seizures in adults as well as in monotherapy in children (in Japan) [66, 69].
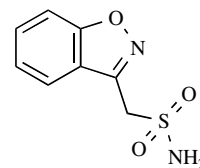
Fig. (4). Chemical structure of zonisamide.

Consistently with multiplicity of mechanisms of action, analgesic activity of ZSM is also diverse. It has been tested in thermal hyperalgesia and mechanical allodynia [70]. Zonisamide is also active in inflammatory and diabetic neuropathic pain. The former was shownwith use of the formalin test, where zonisamide at doses 3 and 10 mg/kg b.w. (mice) reduced licking behavior in both acute and inflammatory phases of the test. The effect was observed after intrathecal administration as well, and the concluded mechanism of analgesia is probably partially peripheral [20]. Analgesic use in various (not specified) neuropathic pain syndromes in clinics has been reviewed, confirming its activity at doses 100 mg/day [67]. As a consequence of its sulfonamide moiety, the drug is contraindicated in patients with allergies to sulfonamides, and may cause serious side effects such as epidermal necrolysis, Stevens-Johnson syndrome, leucopenia, and aplastic anemia, as well as abnormal thinking, dizziness, nausea, headache, *etc.* [67].

Topiramate

Topiramate (2,3:4,5-bis-*O*-(1-methylethylidene)-β-*D*-fructo-pyranose sulfamate, TPM) (Fig. **5**) exerts activity *via* multiple mechanisms. They are inhibition of sodium channels [71] and antagonism of AMPA/kainite (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor [72] as well as enhancement of $GABA_A$ receptor action, inhibition of L-type calcium channels, and inhibition of carbonic anhydrase (similar to zonisamide, this activity does not contribute to anticonvulsant properties). The activity in MES is supported by ED_{50} 15.8 mg/kg b.w. (rats, *p.o.*) and 47.6 mg/kg b.w. (mice, *p.o.*) [71]. Moreover, in experimental epilepsy models the ED_{50} for MES in mice, *p.o.* is 47.6 mg/kg b.w. and in rats, *p.o.* it is 15.8 mg/kg b.w. The dose 20 mg/kg has proved effectiveness in neuroprotective studies in the stroke model [73]. It is indicated in partial and generalized seizures, as well as in intractable childhood epilepsies, at doses 125-400 mg/day for children age 2-16 years (not to exceed 800 mg/day) – Lennox-Gastaut Syndrome (ED_{50}=5.1-5.8/mg/kg/day), West syndrome at 15-29 mg/kg/day, and in monotherapy. Adverse events are somnolence, anorexia, fatigue, attention difficulties, aggression and weight loss. Neuropsychiatric events are less frequent in children than in adults, and they can be managed by slow titration [74].
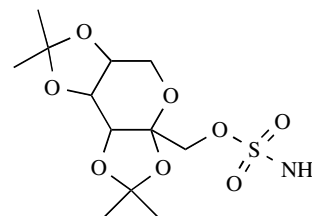
Fig. (5). Chemical structure of topiramate.

The estimated ED_{50} for topiramate's anti-allodynic effect is 30/mg/kg b.w., rats, *i.p.* Chronic constriction injury was also performed in rats at 20 mg/kg b.w., *i.p.*(Table **1**) [73, 75]. Clinical proof of effectiveness in pain indication has been reviewed, describing positive results in clinical trials regarding trigeminal neuralgia (also in multiple sclerosis patients), intercostal neuralgia, and various neuropathic pain syndromes, consistently with CCI models result [67]. Effectiveness in DNP was once proved – the activity was reported at dose range 50-400 mg/day [76], but in other trials topiramate failed [77]. Most common observed adverse effects are: mild asthenia, dry mouth, irritability, diarrhea, fatigue, sedation, nausea, abdominal cramps, and cognitive impairment [67].

Biaryl Pyrazoles

A bis-trifluormethyl derivative (1-[3-[2,5-bis(trifluoromethyl) phenyl]phenyl]-5-methyl-pyrazole-3-carboxamide) (Fig. **6**) has been selected from the group of molecules tested by Merck. The compound is active in 90% in MES, mice, *p.o.* at 10 mg/kg b.w. [78].
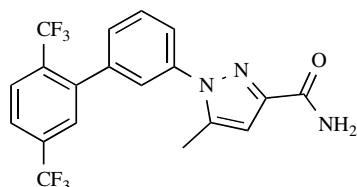
Fig. (6). Chemical structure of 1-[3-[2,5-bis(trifluoromethyl)phenyl] phenyl]-5-methyl-pyrazole-3-carboxamide.

In the spinal nerve ligation model in rats (the Chung model) – with binding preferences toward calcium and potassium channels, as well as sodium channels (IC_{50} for $Na_V1.7$ of 0.810 μM). The activity in Chung model was measured 2 h and 4 h after administration, with 44 and 34% SNL reversal, respectively [79]. The compound is still in preclinical phase.

Gabapentin

Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) (Fig. **7**) is a GABA derivative. Its main mechanism of action, through binding to α2δ subunit, is inhibition of voltage-gated calcium channels. The additional mechanism is related with the above, *i.e.* inhibition of glutamate release, relieving neuronal hyperexcitability [80, 81]. It is a well known antiepileptic drug with proved preclinical and clinical efficacy in epilepsy and pain. Its MES ED_{50} is 78.2 mg/kg b.w. (mice, *i.p.*). It is also active in audiogenic seizures with ED_{50}=2.5 mg/kg b.w. (DBA/2J mice, *p.o.*) and hippocampal kindling with the lowest effective dose 30 mg/kg b.w. (rats, *i.p.*), as well as clonic seizure model with use of metrazole (MET) ED_{50}=47 mg/kg b.w. (mice, *i.p.*) and 52 mg/kg b.w. (mice, *p.o.*) [82]. Its clinical efficacy is proved in adjunctive therapy in partial seizures (by Pfizer) at doses 600-1800 mg/day [83, 84], also with paediatric patients [85]. The main adverse event observed is transient drowsiness [84]. It is inconsistent with preclinical efficacy with MET-evoked seizures prevention, that gabapentin is inactive in absence epilepsy (tested in children) [86].
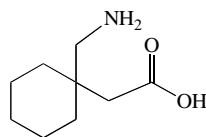
Fig. (7). Chemical structure of gabapentin.

Gabapentinhas become a standard medication for neuropathic pain. However, its analgesic activity is based on a glutamate-dependent mechanism in the brainstem (*locus coeruleus*) [87]. In some reports it is used as a positive control in the SNL model, ad-

ministered *s.c.* to rats [25, 88]. It significantly reduces spontaneous activity of spinal neurons in the Chung model at doses 10-100 mg/kg b.w. [25], while ED_{50} in another research is 32 mg/kg b.w. (Table **1**) [30]. In most clinical trials gabapentin was used at daily doses of 1200 mg or more – the dosage started at 300 mg/day and was titrated until reaching 1200, 2400, or 3600 mg/day. Many studies for the treatment of neuropathic pain syndromes such as DNP and PHN were successful [89-95]. Additionally, the drug is an effective treatment for cancer-related neuropathic pain [96, 97]. Recently, extended release of gabapentin proved effective and well tolerated for the treatment of diabetic polyneuropathic pain [98].

Retigabine

Retigabine (D-23129, ethyl *N*-[2-amino-4-[(4-fluorophenyl) methylamino]phenyl]carbamatic acid ethyl ester, ezogabine) (Fig. **8**) has been documented to exert its anticonvulsant action *via* multiple mechanisms. There is evidence indicating that it increases GABAergic transmission in the central nervous system and activates K_V7 potassium channels [81, 99, 100]. Such various mechanisms result in broad protection against seizures in MES, ScMET (*s.c.* metrazol-induced seizures), as well as amygdala kindling model considered as a model for epileptogenesis [101]. The MES ED_{50}s are 9.3 mg/kg b.w. (mice, *i.p.*) and 2.9 mg/kg b.w. (rats, *i.p.*). Other ED_{50}s are: 13.5 mg/kg b.w. (ScMET, mice, *i.p.*), and 18.6 (ScPic, subcutaneous picrotoxin, mice, *i.p.*) [102]. It was tested in clinics at doses 600 and 900 mg/day as well as 600-1200 mg/day as an adjunctive therapy for partial onset seizures and these doses proved effectiveness [103, 104]. Most commonly reported adverse events were dose-related and included dizziness, somnolence, headache, and fatigue.
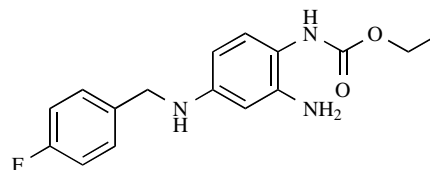
Fig. (8). Chemical structure of retigabine.

Retigabine has been proved to reduce nociceptive behaviors in rat models of neuropathic pain – chronic constriction injury and spared nerve injury. It also exerts analgesic activity in the formalin test (Table **1**) [105, 106]. The assays confirmed antinociceptive activity in models of persistent pain, with concomitant unaffected normal nociceptive sensory processing. This AED has not entered clinical trials for use in pain.

Pregabalin

Pregabalin (CI-1008, (*S*)-3-aminomethyl-5-methylhexanoic acid) (Fig. **9**), is a derivative of GABA. One of the newest mechanisms found for pregabalin is binding to the α2δ subunit of the calcium channels. Similarly to gabapentin, pregabalin is expected to increase GABA concentration in neuronal tissues. It also enhances activity of glutamate decarboxylase. It is active in MES at ED_{50}s of 20 mg/kg b.w. (mice, *p.o.*) and 1.8 mg/kg b.w. (rats, *p.o.*). Activity in audiogenic seizures (Frings mice) also has been proved at doses 3 and 10 mg/kg b.w. *p.o.* (Table **1**) [101]. A recent review found 38 randomized clinical trials related with pregabalin and its use, with the most common dose of 330 mg (controlled release) [107]. The most typical adverse events included dizziness, vertigo, incoordination, balance disorder, ataxia, diplopia, blurred vision, and sleep disorders [107, 108]. Moreover, pregabalin is contraindicated in juvenile myoclonic epilepsy as it can worsen seizures [109].

Pregabalin is active in the Chung model for mechanical allodynia at doses 3-30 mg/kg b.w. (rats, *p.o.*) [110]. Then, numerous controlled clinical trials have shown the efficacy and safety of pregabalin in patients with painful DPN or PHN. In the studies the

patients who received pregabalin at dosages of 300 mg/day [111 - 113] or 600 mg/day [112-115] experienced significant reductions in pain compared with placebo. Recently, flexible-dose pregabalin (150-600 mg/day) led to a statistically significant reduction in pain scores in patients with neuropathic pain due to DPN, PHN or post-traumatic nauropathic pain [116, 117]. Pregabalin 150 to 600 mg/day was also shown to reduce pain in older patients (age ≥ 65 years) with neuropathic pain [118].
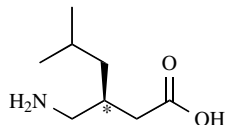

Fig. (9). Chemical structure of pregabalin.

Pregabalin, as Lyrica™, is marketed for the treatment of peripheral and central neuropathic pain in adults. The treatment can be started at a dose of 150 mg/day for treating neuropathic pain. Based on individual patient response and tolerability, the dosage may be increased to 300 mg/day after an interval of three to seven days, and if needed, to a maximum dose of 600 mg/day after an additional seven-day interval [3].

2. GABA Modulators

Influence on GABAergic system can be performed *via* multiple mechanisms: binding to GABA receptors (ionotropic or metabotropic), enhancement of GABA synthesis through GAD (*L*-glutamic acid decarboxylase) activation (in case of valproic acid), or inhibition of GABA catabolism:

- inhibition of GABA-T (γ-aminobutyric acid transaminase) shown by valproic acid and vigabatrin,

- inhibition of SSADH (succinic semialdehyde dehydrogenase) by valproic acid, or

- inhibition of GAT-1 (γ-aminobutyric acid transporter) exhibited by tiagabine [119].

As it can be noticed, it usually appears as a mixture of mechanisms.

Valproic Acid Derivatives

Valproic acid (2-propylpentanoic acid, VPA) (Fig. **10**) acts by a combination of mechanisms related with GABAergic system enhancement (enhancement of activity of GAD resulting in enhanced synthesis of GABA, and inhibiting GABA metabolism – *via* inhibition of GABA-T and inhibition of SSADH) as well as reduction of NMDA-receptor mediated glutamate excitation, and inhibition of serotonergic system [119, 120]. Valproic acid is one of the most active anticonvulsants, exhibiting ED_{50} in MES 485 mg/kg b.w. (rats, *p.o.*), or 6Hz ED_{50}=126 (mice, *i.p.*) (with protection index TD_{50}/ED_{50} 1.6) [121]. At the same time it is one of the most toxic AEDs (causing hepatotoxicity, teratogenicity, nausea, dizziness, and consequently interactions with other drugs, rash, skin inflammation, *etc.*).

The role of this drug in neuropathic pain treatment is still unclear. Although Kochar *et al.*, revealed that sodium valproate is well-tolerated, and provides significant subjective improvement in DNP [122, 123], Otto *et al.* proved that valproic acid has no effect on pain in polyneuropathy [124]. The position of VPA in treatment is so strong that many efforts have been put to develop its second and third generations, in order to limit the side effects, without loss of activity.

Valpromide (2-propylpentanamide, VPD) (Fig. **10**), the amide of valproic acid, was synthesized as one of the very first valproic acid derivatives due to premises that teratogenic activity was related with carboxylic group of the molecule. Indeed, valpromide is not

teratogenic in VPA-induced teratogenicity model in mice. Valpromide is both active in MES with MES ED_{50}=32 mg/kg b.w. (rats, *p.o.*) and ScMET ED_{50}=59 mg/kg b.w. (rats, *p.o.*). It exhibits protection index MES ED_{50}/TD_{50} =2.7, which shows a more safe, larger therapeutic window than the parent VPA [121].
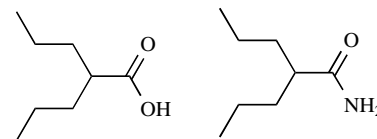

Fig. (10). Chemical structures of valproic acid and valpromide.

Its activity in the SNL model for neuropathic pain is supported by ED_{50}=61 mg/kg b.w. (rats, *i.p.*) [125].

The close analogs of valpromide constitute valnoctamide and valrocemide (*N*-valproyl glycinamide, TV 1901) (Fig. **11**). An interesting fact can be seen when comparing the anticonvulsant activity of the racemate (*R,S*) and 2*R*,3*S* and 2*S*,3*S* enantiomers of valnoctamide with their analgesic results (Chung model) (Table **1**). Racemate seems the optimal configuration for the anticonvulsant activity (MES ED_{50} 29 mg/kg b.w. rats, *i.p.*), when 2*S*,3*S* enantiomer is the most active compound in the Chung model, exhibiting ED_{50} 39 mg/kg b.w. (rats, *i.p.*) [88].

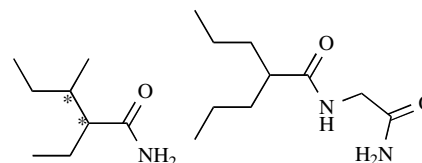Valnoctamide has not been tested in neuropathic pain in humans.

Fig. (11). Chemical structures of valnoctamide and valrocemide.

Valrocemide is a drug candidate in preclinical trials, active in MES with ED_{50} of 151 mg/kg b.w. (mice, *i.p.*), exhibits protection index PI (TD_{50}/ED_{50}) of 2.2. It is also active in ScMet test (mice, *i.p.*) with ED_{50} of 132 mg/kg.b.w. The ED_{50} in rats, *p.o.* is 73.1 mg/kg b.w. in MES (PI>13.7) [126].

Some very interesting discussion can arise from the results of Bialer *et al.* on stereochemical aspects of structure-activity relationship (Fig. **12**). The obtained *R,S*-, *R*-(-), and *S*-(+)-propylisopropylacetamide (PID) reveal various activities in MES (*i.e.* 122, 110, and 145 mg/kg b.w., respectively) in mice, *i.p.*, and 31, 16, and 25 mg/kg b.w., respectively in rats, *p.o.*[127]. These results show that the most potent enantiomer is the *R* one. However, from the therapeutic point of view and taking under consideration extrapolation of results into humans, the differences do not necessarily have to be significant [127, 128].
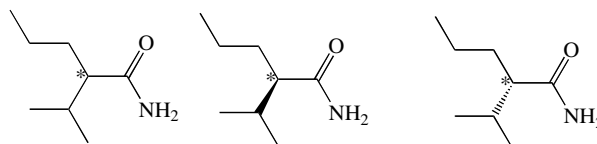

Fig. (12). Chemical structures of racemic PID and its enantiomers (*R,S*, *R*, and *S*, respectively).

Since valrocemide, other valproic acid derivatives have been developed [25], revealing significant activity in neuropathic pain, with primary anticonvulsant mechanism of action. The design of molecules predicted avoiding teratogenicity and hepatotoxicity – the two major disadvantages of the parent compound. The study concerned the following derivatives (Figs. **13** and **14**):

- TMCA (2,2,3,3-tetramethylcyclopropanecarboxylic acid),

- TMCD (2,2,3,3-tetramethylcyclopropanecarboxamide),

- MTMCD (*N*-methyl-2,2,3,3-tetramethylcyclopropane carboxamide),

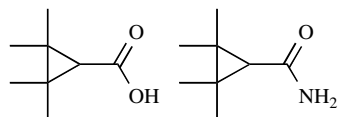- TMCU (2,2,3,3-tetramethylcyclopropanecarbonylurea).

Fig. (13). Chemical structures of TMCA and TMCD.
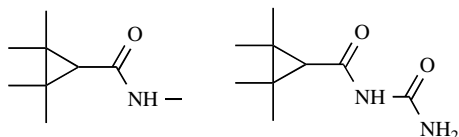
Fig. (14). Chemical structures of MTMCD and TMCU.

They were reported as new valproic acid derivatives. Among them, TMCA showed only weak anticonvulsant activity in rats while others were found to posses broad-spectrum anticonvulsant properties. At the same time all new derivatives: TMCA, TMCD, MTMCD and TMCU showed dose-related antiallodynic activity in SNL model at doses that did not cause motor impairment in the rotarod test [25].

Diisopropylacetamide (DID) (Fig. **15**) is another amide derivative of valproic acid that showed antiallodynic activity in the SNL model. The lowest dose of the compound needed to significantly increase the allodynic threshold was 20 mg/kg (when compared to vehicle) [125].
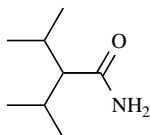
Fig. (15). Chemical structure of DID.

Kaufmann *et al.* reported in 2009 about a wide series of novel amide, *N*-methyl amide and urea derivatives of valproic acid analogues which consists of 17 compounds [129]. All compounds were tested in MES and ScMet in mice after *i.p.* administration as well as in SNL model in rats after *i.p.* administration. Some of them were also evaluated in pilocarpine induced status epilepticus (rats *p.o.*). The neurotoxicity was evaluated as motor impairment or sedation. Compounds possessed five to nine carbon atoms and some of them additionally carried *N*-methyl moiety. In this group, compounds which had 8 carbon atoms showed best activity in both antiallodynic as well as in anticonvulsant tests. At the same time compounds with 9 carbon atoms showed narrower safety margin between antiallodynic activity and motor impairment and sedation although they were more potent antiallodynic agents than 8-carbon atoms derivatives. Compounds with fewer than 8 carbon atoms showed the least anticonvulsant and antiallodynic activity. In the presented group the most promising compounds were 3-methyl-2-propyl-pentanamide and *N*-carbamoyl-2-ethyl-3-methyl-pentanamide exerting good anticonvulsant properties with ED_{50} values in pilocarpine test of status epilepticus of 84 mg/kg (rats, *p.o.*, 0.5 h) and 23 mg/kg, respectively (rats, *p.o.*, 0.0 h). Moreover, 2-isopropyl-3-methyl-pentanamide ED_{50} 50 mg/kg. In a test for neuropathic pain the two first compounds exhibit ED_{50} 49 mg/kg b.w. [129].

Tiagabine

Tiagabine ((*R*)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid) (Fig. **16**) is a derivative of nipecotic acid, used as a hydrochloride, with mechanism of action based on GABA re-uptake inhibition, causing increase of extracellular concentration of GABA. It is more active in ScMET test than in MES, with ED_{50}s 1 mg/kg b.w. (ScMET, mice, *i.p.*), 11.5 mg/kg b.w. (ScMET, rats, *i.p.*) and 4 mg/kg b.w. (ScMET, rats, *p.o.*), compared to 40 mg/kg b.w. (MES, rats, *p.o.*) (Table **1**). Activity in prevention audiogenic seizures is documented by ED_{50} 0.4 mg/kg b.w. (Frings mice, *i.p.*) [130]. It is indicated for use in adjunctive therapy for partial seizures [10].

In a clinical trial for efficacy of TGB as add-on therapy in patients with drug resistant focal epilepsy, tiagabine was administered at dose 30-50 mg/kg as an adjuvant drug to valproic acid or carbamazepine. Beneficial effect of TGB on seizure reduction was seen especially with VA. The most common adverse effects were dizziness and somnolence [131]. Another clinical trial was conducted in patients with refractory epilepsy of whom the mean number of AEDs taken prior to tiagabine was 5. TGB tested at starting dose of 5 or 10 mg/day which was increased another 5 or 10 mg/day every week to achieve the level of 20-40 mg/day. 35% of patients benefited from the drug, mostly with higher doses. The most common adverse effect was dizziness [132].
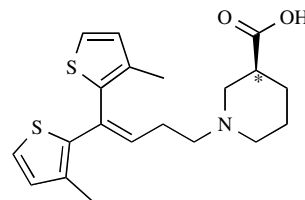
Fig. (16). Chemical structure of tiagabine.

Tiagabine was tested for potential anti-allodynic effects in the nerve ligation (Chung) model of neuropathic pain. The compound showed dose-dependent anti-allodynic and antinociceptive activity in rats, *i.p.*, with significant increases in response threshold to tactile stimulation. In a test for analgesic activity – the formalin test (mice, *i.p.*) – it was active in both acute and inflammatory phase. Nevertheless, it had no effects on carrageenan-induced edema in the same research [133]. Tiagabine has not been tested in clinical trials for use in neuropathic pain.

Vigabatrin

Vigabatrin (4-aminohex-5-enoic acid, VGB) (Fig. **17**) exerts anticonvulsant mechanism of action based on irreversible inhibition of GABA aminotransferase, resulting in increased amount of GABA in the synapse. Vigabatrin is ineffective in the MES and ScMET tests, but it protects against sound-induced seizures and amygdala kindling in mice. It is also active in seizures induced by kainic acid. Further in clinical trials vigabatrin exhibited some activity in drug resistant complex partial seizures, and in the West syndrome. Therefore, VGB is registered for the therapy of partial (focal, local) epilepsy as well as infantile spasms. Still, the side effects represented by this drug are related with increased concentration of extracellular GABA, including peripheral visual field defect or T2 hyperintensities [65, 134].
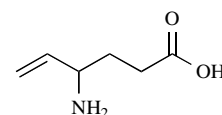
Fig. (17). Chemical structure of vigabatrin.

In order to verify activity of viagabatrin in the Bennett model, a modified procedure of sciatic nerve ligation has been performed

and the activity was observed at the least 10 mg/kg b.w. (rats, *p.o.*). The drug reversed allodynia and hyperalgesia similarly to carbamazepine and valproic acid [135]. The results proved that GABAergic transmission plays role in the mechanism involved in neuropathic pain. More recently, antinociceptive activity of VGB was reported in one of the acute pain models– hot plate test in mice, *i.p.*[136]. However, no clinical trials considering its activity in patients with neuropathic pain have been reported yet and its potential effectiveness needs to be proved in more advanced studies.

3. Synaptic Vesicle 2A Binding Drugs

Levetiracetam

Levetiracetam, (UCBLO59, (S)-α-ethyl-2-oxo-1-pyrolidine acetamide) (Fig. **18**) is the S enantiomer of etiracetam, a pyrrolidine derivative with antiepileptic properties. Although the precise mechanism of action of levetiracetam is not fully understood, the drug appears to bind specifically to synaptic vesicle protein 2A (SV2A) in both brain and spinal cord [137, 138]. 2A protein inhibits calcium release from intraneuronal stores, opposing the activity of negative modulators of GABA- and glycin-gated currents and inhibiting excessive activity between neurons.

Anticonvulsant properties of levetiracetam are untypical – it is inactive in MES, but active in audiogenic seizures in Frings mice and in 6 Hz test in mice. In electroshock kindling (mice, *i.p.*) ED_{50}=7 mg/kg b.w., and in MET kindling – 36 mg/kg b.w. (mice, *i.p.*), in pilocarpine-induced seizures ED_{50}=7 (mice, *i.p.*) [139].
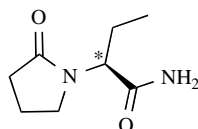

Fig. (18). Chemical structure of levetiracetam.

This AED has been shown to be active in animal models of neuropathic pain. In the chronic constriction injury (Bennett) model the antihyperalgesic effect observed with the compound appeared from a dose of 540 mg/kg whereas in the diabetic rat model at a dose of 17 mg/kg (Table **1**) [140].

Few clinical trials have been conducted to evaluate effectiveness of levetiracetam in the treatment of neuropathic pain and most of those that have been carried out do not show any benefit in comparison to the use of placebo. Levetiracetam failed to relieve peripheral neuropathic pain in postmastectomy pain syndrome (PMPS) at 3000 mg/day [141], the drug was also ineffective in painful polyneuropathy at the same dose [142] and in patients with spinal cord injury (SCI) at 2000 mg/day [143]. This may result from no evidence that SV2A protein would play a role in neuropathic pain etiopathogenesis.

Brivaracetam

Brivaracetam (UCB34714, (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl]butanamide) (Fig. **19**) is a propyl homolog of levetiracetam. Introduction of the propyl moiety changed the ring carbon in position 3 into a chiral one. Brivaracetam, besides binding to synaptic vesicle protein 2A (SV2A) which is its main mechanism [144] also inhibits sodium channels. Just like levetiracetam, this compound is not active in the MES and ScMET tests. Its anticonvulsant activity is supported with ED_{50} in corneal kindling test 1.2 mg/kg b.w. (mice, *i.p.*), in audiogenic seizures 2.4 mg/kg b.w. (Frings mice, *i.p.*), and 6 Hz seizures 4.4 mg/kg b.w., as well as amygdala kindled mice 68.3 mg/kg b.w. and corneal kindling at 1.2 mg/kg b.w. (mice, *i.p.*). In amygdala kindled rats it was effective at ED_{50} 44 mg/kg b.w. (*i.p.*) and 45 mg/kg b.w. (*p.o.*) [81].

This drug is being developed by UCB Pharma, after Phase IIb in which it was well tolerated at doses 50-150 mg/day. It was also

effective in the treatment of focal epilepsy at 100 mg/day in Phase III trial [81]. However, Phase III clinical trial for monotherapy at doses 50 and 100 mg/day was terminated. An interim analysis revealed that the study was unlikely to attain a positive outcome for the efficacy analysis. No safety concerns were detected [145]. Most common adverse events were: aggression, anxiety, irritability, insomnia, depression, convulsion, headache, somnolence, and dizziness [81].
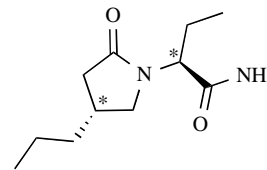

Fig. (19). Chemical structure of brivaracetam.

This AED is also active in CCI models of pain [81] as well asin clinical trials for activity in PHN at 200 mg/day and the study completed in 2010. Unfortunately, no results in humans have been reported until July 2011 [146].

4. Glutamate Receptor Modulators

Both NMDA and AMPA receptors have been considered as interesting targets for potential analgesics active in neuropathic pain. Protection against kainic acid – induced currents suggests neuroprotection. On the other hand, activity on NMDA receptor turns the molecule more towards pain indication [147, 148].

CNS-5161 – NMDA Antagonist

CNS-5161 (N'-(N-(2-chloro-5-(methylmercapto)phenyl)-N′-(3-(methylmercapto)phenyl)-N′-methylguanidine hydrochloride) (Fig. **20**) is a novel and selective noncompetitive antagonist of the NMDA subset of glutamate receptors in the mammalian brain [149, 150]. Preclinical studies have demonstrated compound's anticonvulsant activity [150].
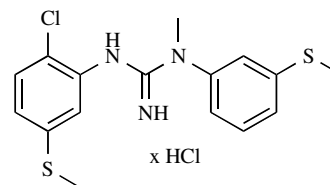

Fig. (20). Chemical structure of CNS-5161.

Consistently with the mechanism of action, the main potential clinical applications of CNS-5161 are analgesia and neuroprotection [151, 152]. In the safety study it was well tolerated up to the dose 0.5 mg and the most common adverse events were hypertension, headache, and mild visual disorders [151]. The study was not sufficiently powered to study analgesic efficacy, although the activity was observed. The compound is being developed by CeNeS (Paion, formerly Cambridge NeuroScience) for the potential treatment of neuropathic pain.

NS-1209 – AMPA Antagonist

NS-1209 (NS-479; SPD-502, [8-methyl-5-(4-(N,N-dimethylsulfamoyl)phenyl)-6,7,8,9-tetrahydro-1H-pyrrolo[3,2-h]-iso-quinoline 2,3-dione-3-O-(4-hydroxybutyric acid-2-yl)oxime] (Fig. **21**) is a water-soluble competitive and potent AMPA/ GluR5 (glutamate receptor subtype 5) selective antagonist [153]. NS-1209 has been found to provide strong protection against status epilepticus induced by electrical stimulation of the amygdala or subcutaneous administration of kainic acid in rats, with bolus injection of 50 mg/kg b.w. followed by infusion of 5mg/kg*h (intravenous, *i.v.*). It is interesting, that so far status epilepticus had been associated with

mechanisms of action like GABA$_A$ antagonism, Na$_V$ channels inhibition, NMDA receptor inhibition, or modulation of calcium influx [154]. At infusions dosing 5mg/kg*h no mortality of animals was observed. Additionally, NS-1209 reveals some neuroprotective activity against status-induced hippocampal neurodegeneration, which, however, was not fully prevented [154].
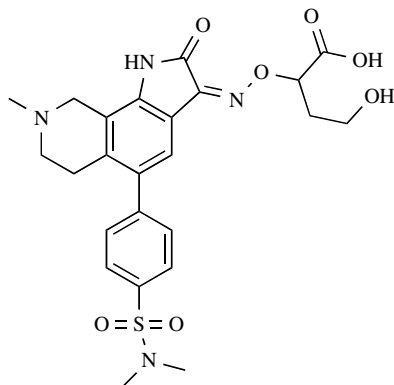

Fig. (21). Chemical structure of NS-1209.

In the chronic constriction injury rat model of neuropathic pain, NS-1209 (3 and 6 mg/kg b.w., *i.p.*) exerts reduction of mechanical allodynia and hyperalgesia responses to von Frey hair and pin prick stimulation of the injured hind paw (Table **1**). The compound was administered to rats 2–7 weeks after sciatic nerve injury. Additionally, injection of NS-1209 produced attenuation of the cold score response after application of ethyl chloride to the injured hind paw [155]. NS-1209's effect on mechanical allodynia is in accordance with the long-lasting *in vivo* effects observed in electrophysiological experiments as described previously [153].

In clinical trials, NS-1209 has been shown to possess a long duration of action and is well tolerated by humans at plasma levels two to four times greater than preclinical levels responsible for neuroprotection in rats. Thus, some of the opportunities for the use of NS-1209 may include an adjunct therapy for the prevention of post-operative pain [155]. One clinical study has been completed for use of NS-1209 and lidocaine for patients with peripheral neuropathic pain – the patients were administered 322 mg of NS-1209 and 5 mg of lidocaine. As a result, both drugs were significantly better than placebo in alleviating brush-evoked mechanical allodynia and they both significantly reduced cold allodynia, but in both allodynias NS-1209 did not differ from lidocaine [156].

Indantadol (CHF3381) – NMDA antagonist

CHF3381 (2-(2,3-dihydro-1*H*-inden-2-ylamino)acetamide hydrochloride, V3381) (Fig. **22**) is a low-affinity, noncompetitive NMDA receptor antagonist and reversible MAO-A (monoaminooxydase) inhibitor. Its MES ED$_{50}$ in rats, *p.o.* is 21 mg/kg b.w. It displayed neuroprotective effects after kainate-induced seizures in preclinical studies, and exhibited anticonvulsant and antihyperalgesic activity [157].
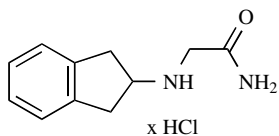

Fig. (22). Chemical structure of indantadol.

The compound was under development by Vernalis plc, under license from Chiesi Farmaceutici SpA, for the treatment of neuropathic pain. It produced a significant suppression of nociceptive behavior and completely blocked mechanical allodynia and hyperalgesia in the capsaicin pain model at 100 and 200 mg/kg b.w. in

rats, *p.o.* [158]. Indantadol was shown to be active in a variety of rodent models of acute, inflammatory, and neuropathic pain. In rats with a sciatic nerve injury (CCI), indantadol relieved both cold and mechanical allodynia (ED$_{50}$ 100 mg/kg, rats, *p.o.*) [159]. Its metabolites are CHF3567 and 2-aminoindane. Its anticonvulsant activity seems stronger than analgesic properties. Still, the analgesic activity in all animal models remains close to the upper limit in the protection gap between ED$_{50}$ in MES and TD$_{50}$ in rotorod=113 mg/kg b.w. (Table **1**) [160].

One clinical trial has been noticed in a Phase II study on safety, tolerability and efficacy of indantadol in DNP at dose 400 mg, but the status of the study has not been updated since 2008 [161].

Tezampanel and NGX-426 – AMPA/Kainate Receptor Antagonists

NGX-426 is the oral ester prodrug of tezampanel (NGX-424, LY293558, (3S,4aR,6R,8aR)-6-[2-(1*H*-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid) (Fig. **23**), although the structure has not been published. Tezampanel and NGX-426 are ionotropic glutamate receptor antagonists that target the AMPA and kainate subtype receptors.Tezampanel is an anticonvulsant and exhibits neuroprotective activity, which is not surprising, taking into account that AMPA receptors are involved in kindling of the amygdala in mice [162].

Tezampanel was tested in rats for activity after plantar incision at dose 34µmol/kg (parenteral). It is interesting that tezampanel failed in a clinical trial for analgesic activity, however, it reduced capsaicin-evoked hyperalgesia in humans. Adverse events observed were hazy vision and sedation [163].

NGX-426 is developed for its analgesic activity only. The compound is under development by Raptor Pharmaceutical (previously Torrey Pines Therapeutics) for the potential treatment of neuropathic pain and migraine in male volunteers.
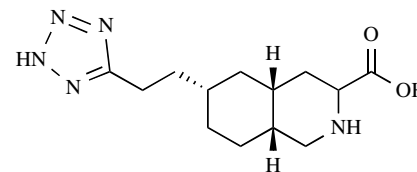

Fig. (23). Chemical structure of tezampanel.

III. CONCLUSIONS

This review shows again that if a drug is active in an animal model, the results cannot be extrapolated to humans directly, and that the risk of failure in clinical trials is significant. Lacosamide can serve as an example, since one clinical trial on DNP failed even though the drug was active in the streptozocin model. This phenomenon is not typical for neuropathic pain, as gabapentin active in MET-evoked seizures in rodents did not show efficacy in absence epilepsy in children.

Considering strategies for drug development, it is already a phenomenon that companies or even researchers turn their drug discovery projects toward a larger market which is pain, due to possible efficacy.These decisions can be seen for *e.g.* CNS-5161 or NGX-426. One reason stated in the introduction is that hyperexcitability of neurons is both a hallmark for epilepsy and neuropathic pain. The reason coming up from the search of the literature is that efficacy, though not always based on the very same mechanism of action in epilepsy and pain, can be expected. Among older drugs, the data show that ED$_{50}$s of drugs presented in the review usually stay in the same range in anticonvulsant and analgesic tests. The newest analgesic drugs, however, have been designed in a way that favors specific analgesic and not antiepileptic profile, probably leading to forthcoming separation of the therapeutic groups.

Table 1.   Anticonvulsant and Analgesic Properties of Selected Anticonvulsants

Figure	Drug Name	Anticonvulsant properties Test ED$_{50}$ (species, route of administration)	Analgesic properties Test ED$_{50}$ (species, route of administration)
1	Carbamazepine	MES 7.81 (mice, *i.p.*) MES 17 (mice, *p.o.*) MES 3.4 (rats, *i.p.*) MES 8.1 (rats, *p.o.*) [10, 27, 34]	SNL 0.5 (rats, *s.c.*)* [30]
1	Oxcarbazepine	MES 14.12 (mice, *i.p.*) MES 6.1 (rats, *i.p.*) MES 10.0 (rats, *p.o.*) [27, 34]	SNL 10 (rats, *i.p.*)* [35]
2	Lamotrigine	MES 7.47 (mice, *i.p.*) MES 3.7 (mice, *p.o.*) MES 1.26 (rats, *p.o.*) AGS 2.39 mice, *i.p.*) hippocampal kindling 61.3 (rats, *i.p.*)** [42, 43]	SNL 12 (rats, *p.o.*) [46]
3	Lacosamide	MES 4.5 (mice, *i.p.*) MES 3.9 (rats, *i.p.*) AGS 0.63 (mice, *i.p.*) [53, 81]	Formalin 32 (mice, *i.p.*) [61]
4	Zonisamide	19.6 mg/kg b.w. (mice, *p.o.*) 7.9 mg/kg b.w. (rats, *p.o.*) [68]	Formalin 3-10 (mice, *s.c.*)* [20]
5	Topiramate	MES 33 (mice, *i.p.*) MES 47.6 (mice, *p.o.*) MES 15.8 (rats, *p.o.*) [71, 164]	CCI 20 (rats, *i.p.*) [75]
7	Gabapentin	MES 78.2 (mice, *i.p.*) MES 14.8 (rats, *p.o.*) [88]	SNL 32 (rats, *i.p.*) [88]
8	Retigabine	MES 9.3 (mice, *i.p.*) MES 2.9 (rats, *i.p*) [81]	SNL >20 (rats, *p.o.*) Formalin 20 (rats, *p.o.*)* [106]
9	Pregabalin	MES 20 (mice, *p.o.*) MES 1.8 (rats, *p.o.*) AGS 3 (mice, *p.o.*)* [81]	SNL 15.9 (rats, *p.o.*) Formalin 4.8 (rats, *p.o.*)* [165]
10	Valproic acid	MES 263 (mice, *i.p.*) MES 829 (mice, *p.o.*) MES 212 (rats, *i.p.*) MES 485 (rats, *p.o.*) 6Hz 126 (mice, *i.p.*) [81, 121, 127]	SNL 269 (rats, *i.p.*) [127]
11	Valrocemide	MES 151 (mice, *i.p.*) MES 73.1 (rats, *p.o.*) [88]	SNL 52 (rats, *i.p.*) [129]
11	*R,S*-Valnoctamide	MES 29 (rats, *i.p.*) [88]	SNL 52 (rats, *i.p.*) [88]
11	2*R*,3*S*-Valnoctamide	MES 34 (rats, *i.p.*) [88]	SNL 61 (rats, *i.p.*) [88]
11	2*S*,3*S*-Valnoctamide	MES 64 (rats, *i.p.*) [88]	SNL 39 (rats, *i.p.*) [88]

(Table 1). Contd…..

Figure	Drug Name	Anticonvulsant properties Test ED$_{50}$ (species, route of administration)	Analgesic properties Test ED$_{50}$ (species, route of administration)
12	*R,S*-PID	MES 122 (mice, *i.p*) MES 31 (rats, *p.o.*) MES 22 (rats, *i.p.*) [127]	SNL 42 (rats, *i.p.*) [127]
12	*R*-PID	MES 110 (mice, *i.p.*) MES 16 (rats, *p.o.*) MES 54 (rats, *i.p.*) [127]	SNL 48 (rats, *i.p.*) [127]
12	*S*-PID	MES 145 (mice, *i.p.*) MES 25 (rats, *p.o.*) MES 49 (rats, *i.p.*) [127]	SNL 46 (rats, *i.p.*) [127]
13	TMCD	MES >250 (rats, *i.p.*) [25]	SNL 85 (rats, *i.p.*) [25]
13	TMCA	MES>150 (rats, *i.p.*) [25]	SNL 181 (rats, *i.p.*) [25]
14	MTMCD	MES 82 (rats, *i.p.*) [25]	SNL 41 (rats, *i.p.*) [25]
14	TMCU	MES 29 (rats, *i.p.*) [25]	SNL 171 (rats, *i.p.*) [25]
15	DID	MES 51 (rats, *i.p.*) [125]	SNL 58 (rats, *i.p.*) [125]
16	Tiagabine	MES 40 (rats, *p.o.*) ScMET 4 (rats, *p.o.*) ScMET 1 (mice, *i.p.*) AGS 0.4 (mice, *i.p.*) [10]	SNL 72.8 (rats, *i.p.*)** Formalin 10 (mice, *i.p.*)* [133]
18	Levetiracetam	electrical kindling 7 (mice, *i.p.*) MET kindling 36 (mice, *i.p.*) [139]	CCI 540 (rats,*i.p.*) Streptozocin 17 (rats, *i.p.*) [140]
19	Brivaracetam	corneal kindling 1.2 (mice, *i.p.*) AGS 2.4 (mice, *i.p.*) 6 Hz 4.4 (mice, *i.p.*) [81]	ND
21	NS-1209	Electroshock seizure threshold increase 50 (mice, *i.v.*) [153]	CCI 3 (rats, *i.p.*) [155]
22	Indantadol	MES 24 (mice, *i.p.*) MES 21 (mice, *p.o.*) MES 7.5 (rats, *i.p.*) MES 21 (rats, *p.o.*) [160]	SNL 100 (rats, *p.o.*)* [160]

*the result is shown as the minimal effective dose MED as the ED$_{50}$ was not determined; ** µMol/kg.
MES – maximum electroshock seizures; AGS – audiogenic seizures; SNL – spinal nerve ligation; CCI – chronic constriction injury; ND – not determined; MET – metrazol, pentyle-netetrazol.

The probable reason for the above mentioned fact is a significant difference in strategiesfor drug discovery in both indications. Since epileptogenesis is a complex process with various causes and epilepsy has multiple symptoms, discovery of anticonvulsants is still performed by screening *in vivo* [10]. As a result, the drugs registered on the market exert multiple mechanisms of action and no specificity towards any ion channel/receptor subtype. Even modern AEDs, such as retigabine, though binds to K$_V$7 channel, also influences GABA system. On the contrary, analgesics are screened *in vitro*, for specific targets such as ion channels, i.e. Na$_V$1.3, Na$_V$1.7 and Na$_V$1.8, or ionotropic glutamate receptors such as NMDA, AMPA, or kainic acid, since the mechanisms of neural damage and induction of neuralgiaare becoming better understood. In such cases there are premises to receive analgesics without anticonvulsant properties, as in the case of *e.g.*NGX-426. It is also a premise to receive better tolerated drugs, exhibiting fewer side effects. In the end, they are hoped to prove effectiveness in the clinical trials and serve as therapy afterwards.

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